THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES.

OCTOBER, 1898.

ANTITOXIN TREATMENT OF PNEUMONIA.[1]

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It is extremely probable that the pneumonic process, as we see it from the moment of invasion to the crisis, implies infection by the agency of a continually changing set of microbes. Welch has shown that the virulence of the coccus is inversely as its age, the organisms taken from the centre of a pneumonic focus having very little potency, while on the edge of a patch which is still spreading they are most active. The inference to be drawn from this, and which is also supported by the behavior of artificial cultures, is that the infection of the system is not maintained through the whole period of pyrexia by the same microbes, but by a constant succession of cocci, the older ones becoming inert, and fresh ones carrying on the work of supplying the toxin. This supply fails soon after the local process has ceased to spread, simply because there are no longer any young bacilli to maintain it. But while it would seem as if this might afford a sufficient explanation of the phenomena of defervescence by crisis, yet the observations of the Klemperers and of subsequent investigators make it reasonably certain that there is an antitoxin produced that has its share in the result. We are apt to think of the process of absorption by which resolution is ultimately effected as beginning *after* the crisis, whereas it is in operation from the first moment of the disease, as is shown by the early infection of the general system which it brings about. Up to the point of consolidation the rate of deposition is far greater than that of removal, and a rapid accumulation of exudate takes place in the air-cells. This exudate, however, is not permanent in constitution. It immediately begins a process of change, and, as we have seen, the organisms contained in it change their properties also. As time goes on there comes a period when the deposition of fresh infective material is less active than the absorption of that which is older. At this point an antitoxic effect becomes apparent, and in the cases terminating by crisis a rapid fall of temperature takes place. In the cases terminating by lysis, either the deposition of fresh material is protracted by the invasion of new territory or the absorption of the older material is for some reason less active.

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[1] Read before the Association of American Physicians, May 5, 1898.

As early as 1888 Netter rendered mice and rabbits immune to pneumonia by injecting them with fluid prepared from the dried spleens of infected animals. Subsequently he employed an old pleuritic exudate containing pneumococci, and at last the sputum of a pneumonic patient which had ceased to be virulent after the crisis.[1]

Pursuing this line of investigation, Foa found that the injection of an attenuated culture of the diplococcus of pneumonia into an animal gave immunity against the disease for several months. He produced the injection serum by precipitating with ammonium sulphate the culture broth containing the diplococci, and filtering repeatedly. The filtrate was injected into the veins of rabbits daily for three or four days. Again, he made an extract of the müscles and viscera of a rabbit dead from pneumonia, precipitated it in the same way, and got the same immunity. The extract from a healthy rabbit when injected gave no immunity.

He then studied the immune animal, drawing the blood and taking the serum after coagulation to inject another animal, which also became immune. As a control experiment, he injected a rabbit with blood of a man dead of pneumonia; death resulted. He states that several species of virus are formed, one seeming to act on the nervous system, another on the blood and tissues.

The Klemperer brothers verified these results.[2] Their report is briefly as follows: Two rabbits were injected, each with 20 c.c. of pleuritic exudate taken from a pneumonic patient and which by culture was shown to be free from living bacteria. Fourteen days later both were inoculated with a virulent culture. Both survived, while the control animal died. Later, they immunized animals with pneumonic sputum taken before the crisis and heated so as to destroy the poison. The same result was obtained by heating to 60° C. a glycerin extract of pneumococci. The bacteria were washed from agar culture with sterilized glycerin, which was exposed to heat for one or two hours and filtered repeatedly. They found that immunity resulted from doses proportioned in quantity to the strength of the preparation. It was employed subcutaneously.

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[1] Centralblatt für klinische Med., 1888, ix. No. 15.

[2] Berliner klin. Woch., August 24 and 31, 1891.

They found further that dogs can be immunized against pneumonia, and can also be cured of the disease. This cure takes place through the serum of immune animals immunized by taking in the products of the activity of the pneumococcus. This immunizing serum does not cure by killing the cocci in the system, for after four days' contact with the serum the bacteria injected into an animal caused death. In fact, the bacteria in contact with this serum increase in number. At the same time the serum, if injected, prevents the formation of the poison in the body of the animal. This may be explained in one of two ways: either the serum hinders their power of forming poison, or the cocci go on forming poison, and the serum counteracts its effects, or through chemical changes renders it inert. At any rate, the cocci become harmless to the animal, their evil influence being destroyed by the reaction of the body cells, especially the white blood-corpuscles. If pneumotoxin and curative serum be mixed and injected into an animal, there is no rise of temperature and no effect from the poison, while toxin alone kills the animal, with symptoms of septicæmia.

They next inquire whether the pneumonia cured in animals by the serum is identical with pneumonia in man. Their autopsies on animals dead of pneumotoxin injections did not show the fibrinous exudation in the lungs characteristic of pneumonia, but diplococci were found in the blood. However, it is not the pneumococci themselves, but the poison that they produce, that gives the septicæmic symptoms. This poison, when formed at the seat of injection, reaches the blood sooner than the cocci themselves. Also, if we filter out the cocci, the poison remaining in solution kills the animal injected as effectually as the original culture.

In contradistinction to animals, man is only slightly susceptible to the pneumoccocus. Living cocci can exist on healthy mucous membranes without doing harm, and are found in the sputum of healthy men. If we inject men subcutaneously, what results do we get? The Klemperers experimented by injecting themselves, and found that no reaction resulted from small amounts; from larger ones a local swelling, with rise of temperature and febrile symptoms, resulted, passing away in a few days. Hence, they conclude that men are much less susceptible than dogs to the same relative doses.

They conclude that in man it is not the exudation in the lung that renders the disease so grave, but the general infection from absorption of the bacterial poisons in the exudate into the circulation, acting on the heart and vital centres, and producing febrile symptoms. In animals injected, the poison enters the blood stream directly and produces fever at once. The poison increases for some days and then the antitoxin is produced, and immunity results. Serum taken from pneumonic patients after the crisis is found to cure pneumonia in dogs. They conclude that from pneumotoxin in man is produced antitoxin at the time of the crisis, and this counteracts the effects of the toxins. Thus the so-called crisis in man is the beginning of the formation of the antitoxin, and though the cocci remain for some time in the blood, they are no longer harmful.[1]

They then question whether immunity in man results after the crisis, and conclude from researches and experiments that it does occur, but is only temporary.

With regard to the treatment of pneumonia, they say at present we use supportive measures, awaiting the formation of antitoxin. But the aged and the weak succumb. They suggest that, by using the immunizing serum from animals, we may hasten this process and save lives. They have treated some cases in this way with apparent benefit, as shown by fall of temperature and slowing of pulse and respiration. But a sufficient number have not as yet been treated to arrive at a definite and final conclusion as to the value of the treatment.

An important discussion on this subject took place at the Academy of Medicine in Turin, December 2, 1892.[2]

Lara, chief physician of the Hospital San Giovanni, reported the results of ten cases of pneumonia under serum-treatment. Five of these cases were double, five single. Eight of the patients were young persons, two advanced in years; six were robust, four of debilitated habit. The serum was in some cases from immunized rabbits, in other cases from dogs, and in still other cases a glycerin extract was employed made from the viscera of refractory animals. In no case was there any local reaction. The glycerin extract produced no observable general symptoms. Serum from dogs caused nervous excitement; that from rabbits produced general agitation and a temporary aggravation of the disease.

In all but three cases there was reduction of temperature, not sudden, but after an interval.

A change in the character of the pulse was observed, without a reduction in the number of beats.

There was no immediate change in the respiration, but, after a time, it became somewhat slower.

The crisis took place in from three to five days. The convalescence was rapid and complete; complications were rare and of little gravity. The reporter considered the results encouraging.

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[1] This statement is not in accord with more recent observations which show that cases in which cocci are found in the blood generally prove fatal.

[2] Journal de Médecine, 1893.

Bozzolo reported five cases treated with serum from rabbits, prepared by a special process not described. There was rapid fall of temperature in every instance. Four of the patients recovered, and one died after defervescence. The kidneys were unaffected.

De Renzi reported that during the past year he had treated ten cases of pneumonia with anti-pneumococcic serum, prepared as follows:

The animals are inoculated with a non-lethal quantity of pneumonia virus, the dose of which is gradually increased until a strong immunity is produced. Serum from these animals is injected into the patient. Only severe cases were selected for treatment. In every case a cure resulted. In one case the temperature came down on the third day, although there were signs of diffuse hepatization. Of five other cases admitted during the year, and not treated with serum, one died. Although the author admits that his cases might have recovered without the serum-treatment, he considers his results decidedly encouraging, as pointing to a real and efficient treatment of pneumonia.[1]

Wiesbecker[2] reports five cases of pneumonia treated with injections of serum obtained from patients recovering from the disease. While there was no uniformity in the results, as far as the objective signs were concerned, these becoming more and more severe in some cases after the injection, while in others the severity abated, there was in every instance a most remarkable improvement in the subjective conditions. This improvement was almost instantaneous, in one case being manifest within one and one-half minutes after the injection. But for one instance, in which the patient was a child only three years of age, we should be inclined to refer these marvellous results to suggestion, especially as they did not conform to the physical conditions present at the moment. Difficulty of breathing, pleuritic pain, malaise of every description disappeared as if by magic; recovery took place in every case, though not always with remarkable promptness. The quantity of serum in each case was 10 c.c.

Similar to this was the experience of Fourriere,[3] in a single case treated by injections of goat's blood. The patient, a person past middle age, was recalled to life from an unconscious, fairly moribund condition, and, though death occurred after several days, there was an interval during which danger seemed to be over and recovery assured.

In 1897 Washbourne, of Guy's Hospital, published his researches on anti-pneumococcic serum. His method was essentially that employed in producing diphtheria antitoxin. A pony was the animal selected, and after nine months' treatment, first with living and then with dead cultivations, the serum was found to possess marked protective powers.

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[1] British Medical and Surgical Journal, March 28, 1896.

[2] Zeitschr. f. klin. Med., 1897, xxxii. p. 188.

[3] Journal de Médecine, January 1, 1893.

By using a special method of cultivation it was found possible to maintain the virulence of the pneumococcus at a given level for a period of sixty-six days. This process is described in detail in the *Journal of Pathology and Bacteriology* for January, 1898. To maintain the virulence of this culture it must be kept in an incubator at a temperature of 37.5° C. He claims that under these conditions the antipneumotoxin can be accurately standardized.[1]

Several cases of pneumonia have been treated by Washbourne and others with this serum. While its influence cannot be distinctly traced, it can fairly be considered to have contributed to the favorable result in some extremely unpromising cases.

We cannot avoid the conclusion, from this résumé of the achievements of serotherapy in its application to pneumonia, that up to the present time they can scarcely be said to amount to more than an encouragement to further effort. No really decisive results have been obtained.

In some cases the effect seems to have been favorable; but, in view of the variable course of pneumonia under all forms of treatment, it is impossible to assign to the injections any positive share in the result. It can be only by the accumulation of a large number of observations that a conclusion as to the value of the treatment can be arrived at, and, unfortunately, the difficulties in the way of extended observations are such as to deter most investigators from pursuing the subject.

The first difficulty is found in the short life of the pneumococcus and its feeble power of resistance. Cocci that are virulent at the beginning of an investigation cease to be so as the investigation proceeds. On the other hand, toxins that are expected to produce only a moderate reaction when injected, sometimes display an unlooked-for virulence. Animals apparently progressing normally toward immunity most unexpectedly succumb to septicæmia from a dose of toxin supposed to be entirely within the limits of safety. Again, animals that were readily immunized at first, lose their immunity in spite of renewed inoculations, and the serum obtained from them ceases to be reliable. This variation in the conditions under which experimentation is conducted is liable to vitiate the most carefully-drawn conclusions. If this be true under the favorable circumstances of the laboratory, what must it be in the exigencies of ordinary practice? If before employing a therapeutic agent we must resort each time to experiment to test the value of the specimen in hand, the usefulness of the agent will be very limited.

It is to be hoped that this difficulty has been overcome by Washbourne's method, already mentioned, and that it will be possible in the future to command a supply of reliable antitoxin for the treatment of pneumonia, as we already do for the treatment of diphtheria. Efforts to produce such a supply are now being made by the Health Board of New York. Should they be successful the value of the method will soon be determined.

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[1] British Medical Journal, 1897.

PRIMARY MALIGNANT DISEASE OF THE SUPRARENAL BODIES.

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A great deal of attention has recently been paid to the nature and origin of suprarenal tumors, and especially of growths derived from outlying bits of the organ, accessory suprarenal bodies, or suprarenal "rests." These latter tumors, which are composed of suprarenal tissue, but are not of the suprarenal body proper, have aroused much interest, because they illustrate so aptly Cohnheim's theory of the origin of tumors from fœtal inclusion, and because when the suprarenal rest is embedded in the substance of the kidney they give rise to a proportion, probably by no means large, of renal growths.[1] But, clinically, the latter cases are, of course, indistinguishable from renal tumors.

Tumors arising in the suprarenal bodies themselves are so near the kidney that they often resemble them clinically, and may easily be mistaken for them. In this paper we propose to record a case of primary malignant suprarenal growth presenting some special points of interest, and to offer some remarks on the general symptomatology and pathology of such cases. For this purpose we append brief notes of five other cases from St. George's Hospital (Table I.) which we have examined microscopically, and of twenty other cases, fourteen of which (Table II.) are collected from literature. And here we would express our indebtedness for references to the papers of Drs. Affleck and Leith in the *Edinburgh Hospital Reports* (vol. iv.), and of Dr. Kelynack, in the *Medical Chronicle* for September, 1897. We have, however, only referred to fourteen cases in literature, which are, we believe, undoubted cases of primary malignant disease of the suprarenal bodies. We have accepted only those which appeared to be certainly primary, and in which the malignant character was shown either by secondary growths or the invasion of adjacent parts. We have, therefore, omitted a number

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[1] Vide Targett (Trans. Path. Soc. London, 1896, vol. xlvii. p. 126), who believes that the frequency of this class of tumors has been much exaggerated by some writers.